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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/273,445	03/19/1999	JAMES K. LIAO	B0801/7137/E	7143

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/273,445	LIAO ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *236-342* is/are pending in the application.

4a) Of the above claim(s) *236-248 and 276-342* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *262-267 and 269-275* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed June 8, 2004 have been received and entered into the application.

Action Summary

The rejection of claims 262-267, 269, 270, 271 and 273 of record under 35 U.S.C. 102(e) as being anticipated by Kaesemeyer (U.S.Patent No. 6,465,516B1) of record is hereby expressly withdrawn in view of Applicants' amendment.

The rejection of claims 268, 269 (limitations directed to capsules, tablets and lozenge), 272 and 273 (limitations directed to capsules, tablets and lozenge) of record under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (U.S.Patent No. 6,465,516B1) of record as applied to claims 262-267, 269, 270, 271 and 273 above, and further in view of Dansereau et al. (U.S.Patent No. 5,622,721) is hereby expressly withdrawn in view of Applicants' amendment.

The rejection of claims 274 and 275 of record under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (U.S.Patent No. 6,465,516B1) of record as applied to claims 262-267, 269, 270, 271 and 273 above, and further in view of Birkmayer (U.S.Patent No. 5,668,114) is hereby expressly withdrawn in view of Applicants' amendment.

Applicants' amendment necessitated the new rejection presented in this Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 262-267 and 269-271 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (U.S.Patent No. 6,465,516B1) of record in view of Ullah et al. (U.S.Patent No. 6,235,311 B1) and further in view of Dansereau et al. (U.S.Patent No. 5,622,721) of record.

Kaesemeyer teaches a method for treating pulmonary hypertension, unstable angina, myocardial infarction and cardiomyopathy, irrespective of the subject's cholesterol level or nonhyperlipidemic comprising administering HMG-CoA reductase

inhibitor including simvastatin. (column 5, lines 1-33, column 10, claims 1-14). Kaesemeyer teaches that HMG-Co-A reductase and L-arginine (a substrate of Nitric Oxide Synthase) set forth in claims 270 and 271 can be combined in a mixture and they may have an unexpected synergistic effect. (column 7, lines 23-45, column 6, lines 8-10). Kaesemeyer teaches that above formulation can be administered as IV (injectable). (column 6, line 30). Kaesemeyer teaches that above composition can be administered orally or intravenously (IV). (column 6, lines 9-31, particularly, line 30).

Kaesemeyer does not expressly teach the sustained release formulation set forth in claim 262 and specified formulations of capsule, tablet, lozenge or injectable preparation set forth in claim 269.

Ullah et al. teach that a pharmaceutical composition comprising simvastatin can be formulated into sustained release formulation in tablets or capsules. (abstract, column 5, lines 35-39, column 7, lines 28-35).

Dansereau et al. teach that sustained-release and delayed release formulations and the dosage formulated in tablets or capsules are well known to those skilled in the art. (column 5, lines 53-59).

It would have been obvious to one of ordinary skill in the art to formulate Kaesemyer's composition to sustained release oral formulation or injectable preparation because Kaesemeyer teaches that the composition comprising simvastatin can be administered orally and intravenously and because the formulations such as sustained-release tablets and capsules are well-known by those skilled in the art by Dansereau et al. Moreover, Ullah et al. teach that simvastatin can be formulated into sustained

release formulation as tablets or capsules. One would have been motivated to formulate Kaesemyer's composition with any one of well-known oral formulation by Ullah et al. in (sustained release) or injectable formulation in order to provide variety of route of administration taught by Kaesemyer and to optimize a formulation appropriate for a subject to be treated.

Claims 274 and 275 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (U.S.Patent No. 6,465,516B1) of record in view of Ullah et al. (U.S.Patent No. 6,235,311 B1) and further in view of Dansereau et al. (U.S.Patent No. 5,622,721) of record as applied to claims 262-267 and 269-271 above, and further in view of Birkmayer (U.S.Patent No. 5,668,114) of record.

Kaesemeyer, Ullah et al. and Dansereau et al. as applied as before.

Kaesemeyer does not teach the nitric oxide synthase cofactors set forth in claims 274 and 275.

Birkmayer teaches that NADPH is useful for the treatment of hypertension. (abstract). Birkmayer teaches NADPH can be formulation in a solid form as tablets, capsules having a delayed release. (column 2, lines 55-68).

It would have been obvious to one of ordinary skill in the art to combine NADPH to Kaesemeyer's composition because NADPH is useful for the treatment of hypertension and NADPH can be formulated into oral delayed formulation. One would have been motivated to make such a modification to achieve at least an additive effect in treatment of hypertension. Absent any evidence to contrary, there would have been

a reasonable expectation of successfully treating cardiovascular disease (e.g. hypertension) of patients disclosed by Kaesemeyer.

Claims 272 and 273 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (U.S.Patent No. 6,465,516B1) of record in view of Ullah et al. (U.S.Patent No. 6,235,311 B1) and further in view of Dansereau et al. (U.S.Patent No. 5,622,721) of record as applied to claims 262-267 and 269- 271 above, and further in view of Moskowitz (U.S.Patent No. 5,385,940).

Kaesemeyer, Ullah et al. and Dansereau et al. as applied as before.

Kaesemeyer does not expressly teach L-arginine in the sustained release system.

Moskowitz teaches L-arginine can be orally administered in sustained release. (abstract, column 3, lines 48-52).

It would have been obvious to one of ordinary skill in the art administered L-arginine co-administered with simvastatin in sustained release formulation because each of active agent can be individually formulated into sustained release formulation as taught by the cited references (Ullah et al. and Moskowitz) and each of the active agents are known to be useful for the same treatment. One would have been motivated to co-administer L-arginine in sustained formulation in order to minimize the dosing frequency and optimize the dosing schedule with simvastatin.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

Applicant's arguments filed June 8, 2004 have been fully considered but they are not persuasive. Applicants argue that there is no suggestion or motivation or suggestion to combine Kaesemeyer and Dansereau, and with regard to claims 274 and 275 neither Kaesemeyer nor Birkmayer disclose the use of sustained, delayed or time-release delivery system. This is not persuasive because the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Kaesemeyer teaches the combination of simvastatin and L-arginine is useful for the treatment of cardiovascular disorder claimed by the Applicants and the combination can be administered orally or intravenously. The oral administration utilizing tablets or capsules in sustained-release formulations are well known by Dansereau and further, simvastatin and L-arginine are well-known to be

formulated in sustained release formulations by Ullah et al. and Moskowitz, respectively. Therefore, it would have been obvious to one of ordinary skill in the art to administer the oral composition taught by Kaesemeyer in any on of oral composition including sustained release formulation. It is also noted that Birkmayer teaches NADPH can be formulation in a solid form as tablets, capsules having a delayed release. (column 2, lines 55-68). Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

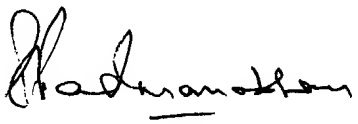
Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Sreenivasan Padmanabhan
Supervisory Examiner
Art Unit 1617

Jmk
September 1, 2004